71. A perioperative genomic profile kit having component parts capable of being assembled for detecting the presence of variant alleles of two or more genes selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β in a subject and thereby providing a subject-specific clinical pathway for said subject, comprising a decision tree that, based at least on the presence or absence of variant alleles of two or more genes selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β measured by said kit, directs a user to a specific clinical pathway of medical intervention for said subject.

REMARKS

Claims 1-23 were filed in the original case. Claims 1-23 were cancelled and Claims 24-44 were added in a previous amendment. Claims 24-44 are cancelled in the present amendment. These cancellations are made without acquiescing to the Examiner's rejections, but are made to further prosecution and Applicant's business interests. Applicant reserves the right to prosecute Claims 24-44 (or similar claims) in the future. Claims 45-71 are added with the present amendment. Therefore, Claims 45-71 are currently pending.

In the Office Action dated January 21, 2003 the Examiner has made two new rejections. The currently pending rejections are:

1) Claims 24-44 stand rejected under 35 U.S.C. 112, second paragraph; and

2) Claims 24-44 stand rejected under 35 U.S.C. 102(b)

Claims 24-44 are cancelled herein, rendering these rejections moot. Applicant believes that the pending Claims are definite, and are not taught by the prior art. Therefore Claims 45-71 should be passed into allowance.

REJECTIONS

For clarity, the rejections at issue are set forth by number in the order they are herein addressed.

I. THE CLAIMS ARE DEFINITE

The Examiner has rejected "Claims 24-44 under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention". Applicant respectfully disagrees. The Examiner argues: "A) Claim 24-44 recite "reagents capable of detecting the presence of variant alleles of two or more genes selected from the group consisting of..." This recitation is indefinite because it is unclear whether the reagents in fact detect the presence of variant alleles of two or more genes." (Office Action 1/21/2003, page 2).

To the contrary, Example 2, "Generation of Genomic Profiles" (Specification, pages 57-58), unequivocally shows, for example, that INVADER and PCR/RFLP assays detect the presence of variant alleles of two or more genes in two thousand one hundred and fifty two (2,152) genotypes from the group *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β as recited by the present disclosure. Therefore it is clear that the claimed reagents provide agents for detecting the variant alleles using, for example, the range of different technologies described in the Specification.

The Examiner also argues "Moreover it is unclear what constitutes a reagent capable of detecting the presence of variant alleles. It is unclear whether the reagent must be used to differentiate alleles of two or more genes, whether the reagent must be any reagent in any chemical assay used." (Office Action 1/21/2003, pages 3-4).

To the contrary, the application is unambiguous regarding "what constitutes a reagent". The CAFC holds:

> "As we have repeatedly stated, claims must be read in view of the specification of which they are a part."[1]

In turn, the Specification is clear regarding "what constitutes a reagent. For example, the Specification provides numerous examples of the nature of reagents that find use in the claimed invention. Several non-limiting examples are provided below:

"In some embodiments, the reagents are INVADER assay reagents." ("Summary of the Invention", Specification, page 6, line 20.)

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[1] *Markman v. Westview Instruments, Inc.*, 34 USPQ2d 1321, 1329 (Fed. Cir. 1995)

and;

"In some embodiments, assays are performed in combination or in hybrid (e.g., different reagents or technologies from several assays are combined to yield one assay)." ("Detailed Description of the Invention - Assays for Generating Genomic Profiles", Specification, page 41, line 3).

and;

"Once so segregated, oligonucleotide probes are synthesized directly on the chip by ink-jet printing of reagents." ("Detection of Hybridization Using "DNA Chip" Assays", Specification, page 45, line 24).

and;

"Secondary reactions are next performed using common reagents for both wild type and mutant assays." (Specification, page 54, line 27).

Pages 40 to 49 of the Specification "Section II. Assays for Generating Genomic Profiles" provide numerous, detailed, definite and clear-cut examples of reagents suitable for the present invention including direct sequencing assays, fragment length polymorphism assays by PCR, RFLP and CFLP, hybridization assays using direct detection and DNA microarrays, enzymatic detection of hybridization, and mass spectroscopy.

In view of the above, Applicant respectfully requests that the rejection be withdrawn.

II. THE CLAIMS ARE NOT ANTICIPATED

A. Prior Art Cited By the Examiner fails the "Each and Every Element" Test

The Examiner has rejected Claims 24-44 as allegedly being anticipated by several references. The Federal Circuit has stated the relevant analysis for anticipation as follows:

> "A claim is anticipated only if each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference."[2]

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[2] *Verdegaal Bros. V. Union Oil of California*, 2 USPQ2d 1051, 1053 (Fed.Cir. 1987)

Applicant respectfully submits that none of the references cited by the Examiner teach each element of the Claims.

The prior art cited by the Examiner consists of pages copied from the catalogs of three manufacturers: Boehringer Mannheim; Perkin Elmer; and Applied Biosystems. For clarity and efficiency, because their defects as prior art are shared, and because the Examiner has cut and pasted from the Boehringer Mannheim text of the Office Action verbatim to the Perkin Elmer and Applied Biosystems text of the Office Action, the three references will be addressed together.

A key flaw in the Examiner's argument for rejection is that the cited prior art does not teach the allele specific elements of the assays of the present Claims. The Specification clearly sets forth the appropriate oligonucleotides and components required to detect the polymorphisms of interest. Conversely, not one of the Examiner's catalogs as a single prior art reference teaches specific reagents sufficient to detect variant alleles in even one of the genes selected from the group *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β. In attempting to remedy this deficiency for one of the cited references (the Boehringer Mannheim catalog) the Examiner impermissibly imports the missing element from thin air: "The label it (sic) thus capable of detecting the presence of variant alleles in hybridization assays using ASO probes, for example." (Office Action, 1/21/2003, page 4). But it is the element of oligonucleotides specific for the alleles of Claim 45 (i.e. the "ASO probes") that is missing from the Boehringer Mannheim reference, and the Perkin Elmer and Applied Biosystems catalogs as well.

None of the three references teaches variant alleles of the genes of the present invention. None of the three references teaches detection of variant alleles in two or more genes from the group of genes of the present invention. None of the three references teaches categorical criteria for the selection of genes and variant alleles of the present invention. None of the three references teaches generation of a perioperative genomic profile.

Applicant respectfully submits that the Boehringer Mannheim, Perkin Elmer, and Applied Biosystems catalog pages cited by the Examiner do not teach each and every

element of the claims as required, and requests that the rejection under 35 USC §102 be withdrawn.

B. Instructions are Essential Elements of the Kits

The Examiner argues "The instructions of the instant kit are not considered to distinguish the claimed kits over the prior art." (Office Action 1/23/2003, page 4) The Examiner also argues: ". . . with regard to the limitation that the kits contain instructions for using said kit for generating said perioperative profile for said subject, the inclusion of instructions is not considered to provide a patentable limitation on the claims because the instructions merely represent a statement of intended use in the form of instructions in a kit." (Office Action 1/23/2003, page 3). Applicant respectfully disagrees. The Examiner's assertions are conclusory, unsupported and legally deficient. In mischaracterizing instructions with "a statement of use" the Examiner cites *In re Haller*, 73 USPQ 403 (CCPA 1947) arguing that "a statement of intended use" is unpatentable. However, *In re Haller* is of no relevance to rejection of the present application. Instructions are not a "statement of intended use", nor are instructions "mere re-labelling" (*In re Haller*, 403). The Examiner mistakenly conflates kit instructions with "an admittedly old compound, labelled for a new use as an insecticide", (id at 403), while *In re Haller* itself does not. Indeed, the terms "instructions" and "kit" fail to appear anywhere in the text of *In re Haller*.

To the contrary, ". . . printed matter, in an article of manufacture claim, *can* be given "patentable weight."[3] (Original emphasis.) The CAFC in *In re Levin* holds:

> "The only requirement that 35 U.S.C. §101 imposes as set forth in In re Miller is that a new and unobvious functional relationship must exist between the claimed combination of printed matter and other claimed elements. 418 F.2d at 1396, 164 U.W.P.Q. (BNA) at 49. For instance, as we have stated in In re Gulack, "the critical question is whether there exists any new and unobvious functional

[3] *In re Miller* 57 C.C.P.A. 809; 418 F.2d 1392.

relationship between the printed matter and the substrate." 703 F.2d at 1386, 217 U.S.P.Q. (BNA) at 404.[4]

Because novel, unobvious functional relationships clearly exist between the claimed instructions and substrate kits, the present invention surmounts the requirements of the *In re Gulack* test. An instruction is "An authoritative direction to be obeyed; an order"; instructions are "Detailed directions on procedure." (The American Heritage Dictionary 3rd Edition, 1993). Clearly instructions do not "merely represent a statement of intended use" as the Examiner alleges (Office Action 1/23/2003, page 3). As physical acts dictating the manipulations of physical objects and activities, instructions of the claimed kits implement a set of actions to accomplish a useful, concrete and tangible result. Instructions embody functional components interacting with the claimed kits in novel modes of cooperation, thereby permitting the kit's functionality to be realized. Under some embodiments of the presently invention, instructions that direct, for example, a treatment course of action utilize physically organized data structures for two or more assays, which are not fixed or determinate beforehand. A patient's preferred clinical pathway cannot properly be executed in advance absent the results of the assay as instructed. Instructions that cause and direct a particular treatment course of action utilize results from two or more genotypes. A combination of markers may well instruct one course of action rather than another.

The Examiner also argues: "Because no patentable weight is given to the written material in the instructions describing a method, the claim is anticipated by the Boehringer Mannheim Catalog". (Office Action 1/23/2003, page 4). Again the Examiner's mischaracterizations are erroneous, and unsupported by any citation to relevant case law, the MPEP, an affidavit or other authority. Instructions of the present Claims are not descriptions as defined by The American Heritage Dictionary 3rd Edition, 1993: a description is defined as "A statement or account describing something". An instruction is "An authoritative direction to be obeyed; an order"; instructions are "Detailed directions on procedure." (The American Heritage Dictionary 3rd Edition, 1993). An instruction and a description are not the same thing. Moreover, the kits of the

[4] *In re Levin*, 107 F.3d 30 (Fed. Cir. 1997).

present claims are articles of manufacture not methods, as misconstrued by the Examiner. Finally, nothing in the written materials copied by the Examiner from the Boehringer Mannheim catalog teaches kits for generating perioperative genomic profiles as instructed under the Claims.

Applicant respectfully submits that none of the Examiner's prior art references or arguments satisfies statutory requirements for rejection under 35 USC §102, and requests that the rejection be withdrawn.

CONCLUSION

All grounds of rejection of the Office Action of January 23, 2003 have been addressed and reconsideration of the application is respectfully requested. It is respectfully submitted that Applicant's claims as amended should be passed into allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

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